REMARKS

Claims 1-26 were pending in this application. Claims 10, 11 and 24 are canceled. Applicants expressly reserve the right to pursue protection of any or all of the subject matter of the canceled claims in a subsequent application. Rejections of canceled claims are hereafter treated as moot. Claims 1, 12, 23, 25 and 26 have been amended. Claims 32-34 are new.

Support for claim amendments and newly added claims 32-34 can be found throughout the specification and the claims as originally filed, for example at least on page 7, lines 3-4; page 19, lines 18-10; Examples 1-4 and originally filed claims 10, 11 and 18. Claim 23 is amended herein to incorporate the limitations of claim 24. No new matter is introduced by these amendments.

After entry of this amendment **claims 1-9, 12-23, 25, 26 and 32-34 are pending in this application**.

Claim Rejections under 35 U.S.C. §103:

Claims 1-26 have been rejected under 35 U.S.C. §103 as allegedly being obvious in light of Ponec *et al.* (*New England J. Med.* 341(3): 137-141, 1999; hereinafter Ponec *et al.*) in view of Vavilala *et al.* (*New England J. Med.* 341(21): 137, 1999; hereinafter Vavilala *et al.*). Applicants traverse this rejection.

Ponec *et al.* disclose the use of neostigmine for the treatment of acute colonic pseudo-obstruction. Acute colonic pseudo-obstruction is massive dilation of the colon without mechanical obstruction that occurs following surgery or acute illness. Ponec *et al.* teach that a side effect of the administration of neostigmine is bradycardia.

Vavilala *et al.* teach that because bradycardia is a complication of neostigmine therapy, another antimuscarinic agent can be administered, such as glycopyrrolate, to minimize such complication. They recommend using glycopyrrolate prophylactically, with continuous monitoring by electrocardiography and blood pressure assessment following neostigmine administration in the operating room.

To establish a *prima facie* case of obviousness, the Examiner must identify all of the claimed elements in one or more prior art references and provide a motivation or suggestion to combine or modify the prior art references coupled with a reasonable expectation of success (MPEP §2143).

The Office has failed to establish a *prima facie* case of obviousness because all of the claim elements are not taught, suggested or disclosed by the cited references. Ponec *et al.* and Vavilala *et al.* both describe treatment in the acute setting. Thus, even if one were to combine Ponec *et al.* and Vavilala *et al.,* one would use neostigmine and glycopyrrolate acutely, with simultaneous electrocardiography and blood pressure assessment. Neither Ponec *et al.* or Vavilala *et al.* disclose, suggest or render obvious "a method of bowel care comprising chronically administering a therapeutically effective amount of a drug combination comprising an acetylcholinesterase inhibitor and an anti cholinergic agent to a subject to relieve chronic constipation in a subject having chronic intestinal pseudo-obstruction, wherein the chronic intestinal pseudo-obstruction is an effect of a spinal cord injury" (claim 1). In addition, neither Ponec *et al.* or Vavilala *et al.* disclose the administration of neostigmine and glycopyrrolate at least one time a week for at least a month (claim 23). Neither Ponec *et al.* or Vavilala *et al.* disclose, teach or suggest methods of bowel care for chronic constipation resulting from chronic pseudo-obstruction in a subject with a spinal cord injury. Because the references cited by the Examiner fail to teach or suggest all of the elements of the claims, such references cannot serve as the basis of a rejection of the claims under 35 U.S.C. §103(a).

Chronic intestinal pseudo-obstruction is a very different condition from acute intestinal pseudo-obstruction. In contrast, acute intestinal pseudo-obstruction is "a relatively rapid onset, intense, short-term occurrence of intestinal pseudo-obstruction" (see the specification at page 13, lines 4-9). Indeed, acute pseudo-obstruction is a condition that has a rapid onset, and can be a life threatening condition associated with abdominal pain and distension, inability to eat, electrolyte abnormalities and the need for immediate intervention. Chronic intestinal pseudo-obstruction, however, is "persistent, recurring intestinal pseudo-obstruction" (see the specification at page 13, lines 9-10). The inability to eliminate stool from the colon after spinal cord injury is characterized by long-term difficulty with stool evacuation and/or fecal

incontinence that results in a chronic problem that may last for many years. Its management requires usually thrice weekly use of strong laxatives, large numbers of enemas, and potentially traumatic stimulation of the rectum with an assistive device throughout the lifetime of the affected individual. Bowel care after spinal cord injury is required over the lifetime of the patient with spinal chord injury, and often takes up to three hours on each bowel care day and despite this time expenditure, may not be successful. (see Steins *et al. Arch. Phys. Med. Rehabil.* 78: S86-S104, 1997 provided in Appendix A). Thus, acute pseudo-obstruction and chronic pseudo-obstruction are very dissimilar conditions, with very different etiologies and treatment regimes.

Given the teachings of Ponec *et al.* and Vavilala *et al.* on the treatment of acute colonic obstruction and the continuous monitoring used in the operating room, one of skill in the art would not predict that the disclosed therapy would be of use on a chronic basis in a non-clinical setting. As such, Ponec *et al.*, alone or in combination with Vavilala *et al.,* do not teach, suggest, or disclose a method of bowel care for a subject having chronic constipation associated with chronic intestinal pseudo-obstruction.

The specification documents several unexpected results obtained using neostigmine and glycopyrrolate. Specifically, (i) the colonic response to neostigmine is not blunted by glycopyrrolate; and (ii) neostigmine and glycopyrrolate produced prompt and complete evacuation in 64% of subjects, higher than neostigmine alone (57%). In addition, the combination of neostigmine and glycopyrrolate caused less bradycardia than neostigmine alone, and glycopyrrolate counteracts the respiratory side effects caused by neostigmine alone. The documentation of the unexpected superior properties of the combination of neostigmine and glycopyrrolate as compared to neostigmine alone rebuts any *prima facie* case of obviousness.

Based on all of the foregoing arguments, Applicants request that the rejection of claims 1-9 and 12-26 under 35 U.S.C. §103(a) be withdrawn.

Newly added claims:

Newly added claim 32 depends from claim 1. Newly added claims 33 and 34 depend from claim 23. As such, these claims are free of the cited art for at least the reasons mentioned above.

CONCLUSION

It is respectfully submitted that the present claims are in a condition for allowance. If any issues remain, the Examiner is requested to contact the undersigned attorney prior to issuance of the next Office action in order to arrange a telephone interview. It is believed that a brief discussion of the merits of the present application may expedite prosecution and allowance of the claims.

Respectfully submitted,

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